REMARKS

Claims 1 and the claims dependent thereon have been amended to insert the word "an" before "anionic CpG oligonucletide" to correct an inadvertent omission and to place the claims in condition for allowance or appeal. No additional search is provoked thereby. Support for the amendment is found in originally filed claim 1. No new matter ahs been added hereby. Entry thereof is requested.

The claims now pending are: 1, 4-10 and 12-75. The Examiner had withdrawn claim 10 as not being directed to the species elected. However, Applicant wish to point out that in a species election, claims directed to a non-elected species are not considered withdrawn. Claim 1 as presented in a generic claim and embrace within its scope all of the species. Therefore, it is believed that claim 10 remains pending. Applicant considers the rejection made was for all of the pending claims including claim 10. The remarks below are also applicable thereto.

Response to Rejections under 35 U.S.C. §103(a)

Rejection of claims 1, 5, 7-9, 12-13 and 18-19

Claims 1, 5, 7-9, 12-13, and 18-19 are rejected under 35 U.S.C. §103(a) as unpatentable over Krieg et al in view of Ladd et al. "as evidenced by result no. 1 of the rng [sic] and result no. 1 of the rag search summary pages".

To establish a prima facie case of obviousness, it the burden of the Examiner to prove that each and every element of the claim has been met by the disclosure, teaching or suggestion in the prior art, or the prior art as a whole when placed before the skill in the art at the time invention was made would render the claimed invention obvious. In carrying out this burden, it is impermissible to use the disclosure or teaching of the applicant.

The claims now pending are directed to a stabilized immunostimulatory microparticulate complex comprising a cationic peptide immunogen that comprises a target B cell antigen or a CTL epitope and a T helper cell epitope in combination with an anionic CpG oligonucleotide. The CpG oligonucletide is anionic at a pH in the range of 5.0 to 8.0. The

specification describes how to determine the anionic charge of the CpG oligonucleotide by examining the presence of phosphodiester or phosphorothioate groups, each of which is assigned a charge of -1. It is important to recognize that the phosphodiester in a backbone of a CpG oligonucleotide is unstable. Thus, the CpG oligonucleotide may be modified to obtain a negatively charged moiety by the addition of a phosphorothioate group.

A careful review of Krieg et al. shows that Krieg et al is directed to Pyrimidine rich, preferably thymidine rich oligodeoxynucleotides (ODN) which do not require a CpG motif. Krieg et al teaches that such pyrimidine or thymidine rich ODNs are immunostimulatory. Krieg et al provided numerous examples of ODNs as immunostimulatory. Nowhere in the 156 pages of the specification or the 105 claims is the word "anionic" to be found. Krieg et al does not disclose, teach or suggest how to determine if a CpG oligonucleotide is anionic at a pH of 5.0 to 8.0 nor how to modify it if it were not anionic. More important, Krieg et al. does not disclose, teach or suggest a method of rendering the CpG oligonucleotide anionic by modifying the CpG oligonucleotide with a phosphorothioate group to convert it to a stable anionic oligonucleotide if it is not. There is no teaching, disclosure or suggestion in Krieg et al of the use of an anionic CpG and to form a stabilized immunogen with a cationic peptide.

Also, there is no disclosure, teaching or suggestion in Krieg et al. of how to select a peptide that is cationic nor how to render the peptide cationic by modifying the peptide with the addition of lysine, arginine, or histidine at the N- or C-terminal.

As proof of the finding of obviousness, the Examiner points to the nucleic acid sequence of SEQ ID NO:1, which is 5'TCGTCGTTTTGTCGTTTTGTCGTTTTGTCGTT-3' with 32 nucleotides and contends that it has a negative charge of -32 at a pH of 5.0 to 8.0. There is nothing in Krieg et al. that teach or suggest that such a nucleotide has a negative charge, not remotely a negative charge of -32. However, there is nothing in Krieg et al about the charge of an ODN. Moreover, there is nothing in Krieg et al. to indicate that the ODN is negatively charged by counting the nucleotides in an ODN.

In fact, Krieg et al. teaches that some ODN are immunostimulatory and some are not. It is by testing each ODN to see if they have the ability to be immunostimulatory. See page 130 of Krieg et al. According to Krieg et al, the stimulatory effects are due to the presence of TG and not simply those of a phosphorothioate backbone. Based on this statement, Krieg et al.

teaches against the addition of phosphorothioate moiety to the backbone of a CpG oligonucleotide.

A review of Ladd et al. shows that there is no disclosure , teaching or suggestion of CpG oligonucleotides. Thus, there is nothing in Ladd et al. about how to determine whether a CpG oligonucleotide has a negative charge nor how to modify it if is not negatively charged.

There appears no basis for the Examiner's determination that SEQ ID NO: 1 has a -32 negative charge. If it is as the Examiner contends that each nucleotide has a negative charge of -1 at pH of 5.0 to 8.0, there has to be something in the prior art cited to provide a basis for this finding. It is to be noted that the Applicant has indicated a +2 charge for the cationic peptide is preferable. It would defy scientific principles to be able to form a stable immunogen with 16 to 32 cationic peptide to one CpG oligonucleotide.

It appears that this finding of negatively charged CpG oligonucleotides is based on applicant's discussion of how to determine if a CpG oligonucleotide is negatively charged. However, Applicant wish to point out that the specification teaches at page 16 [0037], that the negative charge of the CpG oligonucleotide is based on the presence of a phosphodiester or a phosphorothioate group not the nucleic acids in the CpG oligonucleotide sequence itself.

There is nothing in Krieg et al. with respect to the combination of an anionic CpG oligonucleotide with a cationic peptide comprising a B cell epitope or a CTL epitope and a T helper epitope. There is nothing in Krieg et al on how to determine if a peptide is cationic or how to render a peptide to be cationic. A review of Ladd et al. also shows that there is nothing in Ladd et al about a cationic peptide nor how to render a peptide to be cationic. Ladd et al does not disclose, teach or suggest what makes a peptide cationic nor how to make a peptide cationic by adding a lysine, arginine or histidine to its N- or C-terminal.

The use of an anionic CpG oligonucleotide in combination with a cationic peptide is disclosed by Applicant.

A review of the case law governing a finding of obviousness clearly shows that it is impressible to view prior art by reading into it the teachings provided by the Applicant. The Supreme Court stated in a recent case:

> "A fact finder should be aware, of course of the distortion caused by hindsight bias and must be cautious of arguments

> reliant upon ex post reasoning." KSR Int'l Co. v Teleflex Inc. 127 S. Ct. 1727, 1742 (2007).

The Supreme Court's cautionary words reflect long standing case law. In In re Sporck, where the sole issue was obviousness, the Board of Appeals had concluded that the modification was an obvious adaptation over the prior art because it appeared to be a very simple modification. However, the Court of Customs and Patent Appeals held that:

> "Neither the record nor the facts judicially noticeable supplied the factual data necessary to support the legal conclusion of obviousness at the time the invention was made without substitution and hindsight appraisal of the prior art for such factual data...Once appellant's solution to the problem of making a tapered wall frusto-cone is disclosed, it is easy to see how the prior references can be modified and manipulated to produce this type of cone....However, the simplicity of new inventions is often times the very thing that is not obvious before they are made." In re Sporck, 301 F.2d 686, 689 (CCPA 1962).

The MPEP Section 2143 reflects the holding of these case decisions and states:

> "The teaching or suggesting to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." citing In re Vaeck, 947 F.2d 488. 20 USPQ 2D 1438 (Fed. Cir. 1991)

In the present case, how to select or obtain an anionic CpG oligonucleotide is not found in the cited prior references Krieg et al or Ladd et al. The selection or obtaining a cationic peptide is not found in the cited prior references Krieg et al or Ladd et al. The formation of a stable immunogen complex using the selected or modified CpG oligonucleotide with a selected or modified peptide with a positive charge is not found in the cited prior references Krieg et al or Ladd et al. How to select or obtain an anionic CpG oligonucleotide and a cationic peptide to

form a stable immunogen complex is found in Applicant's disclosure. Furthermore, it is surprising that by forming microparticles of the stabilized immunogen complex, a higher titer of antibodies is obtained. See results shown in Figs 7 and 9. Moreover, the virus neutralization activity of the antibodies elicited is improved.

Rejection of Claims 1, 4 and 6

Claims 1, 4 and 6 were also rejected as being obvious in view of Krieg et al and Ladd et al for the same reasons.

Reconsideration of the rejection is requested. As stated above, it is impermissible to apply the Applicant's disclosure to the cited references to support a finding of obviousness.

For the reasons stated above, it is believed that the burden of proof of a prima facie case of obviousness relying upon the cited references, Krieg et al. and Ladd et al.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 1151-4172.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 1151-4172.

Respectfully submitted,
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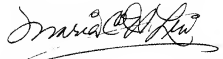
Dated: December 18, 2007 By: 

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